A Facile One-Pot Synthesis of 4-Hydroxy-3-nitro-2-methyl-(2H)-1,2-benzothiazine 1,1-dioxide

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Summary: Herein the synthesis of 4-hydroxy-3-nitro-2-methyl-(2H)-1,2-benzothiazine1,1-dioxide is described in a novel one-pot reaction. The synthesis involved two transformations starting from 2-methyl-2H-1,2-benzothiazin-4-(3H)-one 1,1-dioxide, with an overall yielded better than that from the stepwise process starting from saccharin. One-pot synthesis of an important intermediate, nitromethyl saccharin is also described.

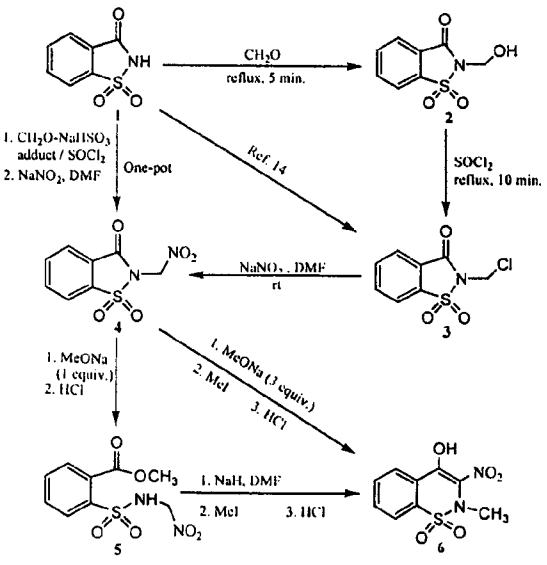
Introduction

Benzothiazine derivatives such as, piroxicam [1], meloxicam [2], droxicam [3], ampiroxicam [4], sudoxicam [5] and cinnoxicam [6], are the well known oxicam drugs to possess potent biological activities. The importance of benzothiazine stems from the fact that since time of its first synthesis by Braun *et al.*, [7], in 1923, thousands of its derivatives have been synthesized and found to be biologically active as analgesic [8], antipyretic [9], hypoglycemic [10], antihypertensive [11], anti-inflammatory [12] etc. In all these molecules, 1,2-benzothiazine 1,1-dioxide is mainly substituted at 2-, 3- or 4-position of the thiazine nucleus.

As a part of our ongoing research program to develop new anti-inflammatory agents, we needed 4-hydroxy-3-nitro-2-methyl-(2H)-1,2-benzothiazine 1,1-dioxide (**6**). To the best of our knowledge, no work has been reported on such types of compounds, and therefore, which forms the basis for these studies.

Results and Discussion

First, we carried out the preparation of nitro-methylsaccharin (**4**) in a three-step process (hydroxy-methylation, chlorination and sulfonation), where each step was studied separately with the idea of designing a one-pot procedure. Reports on N-alkylation of sodium saccharin quoted yields up to 70 % in aqueous phase in literature [13]. We synthesized N-hydroxymethyl saccharin (**2**) up to 92 % yields from insoluble saccharin (**1**) by reaction with formalin (37 %). Chlorination of (**2**) with thionyl chloride [14], under anhydrous conditions afforded N-chloromethyl saccharin (**3**). Nitration of (**3**) was achieved by treatment with sodium nitrite [15] to yield nitro-methylsaccharin (**4**), in good yield (Scheme-1).



Scheme-1

On the basis of known facts developed in the step-wise process, the possibility of direct conversion of (**1**) into (**4**) in one-pot was explored. It provided (**4**) in good yield. The cleavage of the heterocycle in (**4**) was achieved by treatment with sodium

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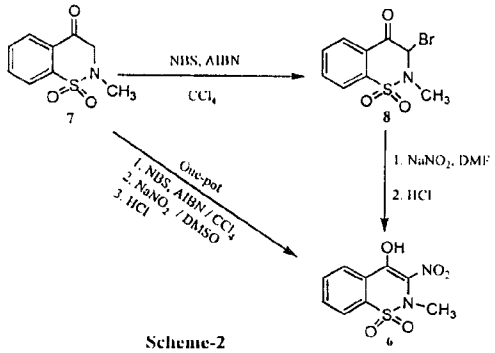
methoxide (1 equiv.) in methanol to get (**5**) in 94 % yield. Cyclization of the latter, followed by *in-situ* N-methylation accomplished the synthesis of (**6**). Direct conversion of (**4**) into (**6**) *via* Gabriel-Colman rearrangement was also carried out, using same metal alkoxide (3 equiv.).

Further, we devised an excellent route toward synthesize (**6**) from 2-methyl-2H-1,2-benzothiazin-4-(3H)-one 1,1-dioxide (**7**) [16]. Bromination of (**7**) by N-bromosuccinimide with azoisobutyronitrile [17] in carbon tetrachloride, and subsequent nitration of (**8**) confirmed the synthesis of (**6**). Finally, a direct conversion of (**7**) into (**6**) in one-pot was also successful (Scheme-2).



Scheme-2

Experimental

Melting points were recorded on a Gallenkemp apparatus and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker DPX-400 instrument at 400 and 100 MHz, respectively, in DMSO or otherwise the solvent that is mentioned. Chemical shifts were reported as δ in ppm using tetramethylsilane (TMS) as internal reference standard. IR spectra were recorded on a Perkin Elmer 1600-FT spectrometer. Mass spectra were recorded on a Jeol SX-102 instrument.

N-hydroxymethyl saccharin (2)

A mixture, of (**1**) (5 g, 27 mmol) and formalin (5 ml, 67 mmol) in water (15 ml), was heated under reflux for 5 min. [18], cooled to room temperature and filtered. The solid was washed with cold water and dried to produce (**2**) (5.4 g, 25 mmol, 92 %); mp 136-137 °C (lit. 137-141 °C); ν_{max} (KBr) 3280, 1745, 1175, 1055 cm^{-1}; ^{1}H-NMR *δ*: 8.26-7.92 (4H, m, aromatic), 5.19 (2H, s, CH_2), 2.05 (1H, s, OH); EIMS *m/z*: 213 [M$^+$], 196 [M$^+$- OH]

N-chloromethyl saccharin (3)

A mixture, of thionyl chloride (10 ml) and (**2**) (5 g, 23 mmol), was heated under reflux for 10 min, and an excess of the reagent was distilled out. The residue was dried overnight to obtain (**3**) (4.8 g, 20.5 mmol, 89 %); mp 137-138 °C (lit. 140-142 °C); ν_{max} (KBr) 1755, 1180, 1052 cm^{-1}; ^{1}H-NMR δ: 8.10-7.84 (4H, m, aromatic), 5.25 (2H, s, CH_2); EIMS *m/z*: 231.4 [M$^+$], 196 [M$^+$- Cl]

N-nitromethyl saccharin (4)

N-chloromethyl saccharin, (**3**) (0.25 g, 1.0 mmol) and sodium nitrite (0.30 g, 4.0 mmol), in dimethylformamide (25 ml), were stirred at room temperature for 12 h, diluted with cold water (25 ml) and filtered. The residue was extracted with ethyl acetate and the extract evaporated to give (**4**) (0.05 g, 0.2 mmol, 21 %); mp 164-165 °C; ν_{max} (KBr) 3260, 1735, 1550, 1360 cm^{-1}; ^{1}H-NMR δ: 8.23-7.26 (4H, m, aromatic) 6.20 (2H, s, CH_2); ^{13}C-NMR *δ*: 80.7, 126.3, 128.2, 128.9, 133.1, 133.9, 141.7, 169.1; EIMS *m/z*: 242 [M$^+$], 196 [M$^+$- NO_2]; Anal. Calcd. for $C_8H_9N_2O_5S$: C, 39.67; H, 2.50; N, 11.57; S, 13.24. Found: C, 39.66; H, 2.51; N, 11.57; S, 13.20.

One-pot synthesis of N-nitromethyl saccharin (4)

A mixture of (**1**) (1.72 g, 9.4 mmol), formaldehyde-sodium bisulfite adduct (6.31 g, 47.0 mmol) and thionyl chloride (15 ml) was refluxed gently overnight. Excess thionyl chloride was removed under vacuum. Sodium nitrite (2.28 g, 33.1 mmol) in dimethylformamide (40 ml) was added and stirred at 60 °C for 4 h, diluted with cold water (200 ml) and filtered. The residue was extracted with ethyl acetate and dried to give the product (**4**) (0.71 g, 2.9 mmol, 31 %); mp 164-166 °C

Methyl [2-(nitromethyl)sulfamoyl]benzoate (5)

Nitromethyl saccharin (**4**) (1.0 g, 4.1 mmol) was added to a solution of sodium methoxide (0.25 g, 4.5 mmol) in dry methanol (15 ml). The reaction mixture was heated under reflux for 30 min., cooled to room temperature and acidified to pH = 3. The solid was filtered, washed with cold water and dried to produce (**5**) (1.06 g, 3.9 mmol, 94 %); mp 97-98 °C; ν_{max} (KBr) 3450, 3295, 1680,1560, 1375 cm^{-1}; ^{1}H-NMR *δ*: 8.26-7.39 (4H, m, aromatic), 6.25 (2H, s , CH_2), 3.35 (3H, s , CH_3), 2.01 (1H, s , NH); ^{13}C-NMR δ: 52.1, 82.3, 128.3, 131.3, 132.0, 132.3, 134.9, 141.3, 168.1; EIMS *m/z*: 274 [M$^+$], 214 [M$^+$-

CH_2NO_2]; Anal. Calcd. for $C_9H_{10}N_2O_6S$: C, 39.42; H, 3.68; N, 10.21; S, 11.69. Found: C, 39.43; H, 3.66; N, 10.22; S, 11.68

4-hydroxy-3-nitro-2-methyl-(2H)-1,2-benzothiazine 1,1-dioxide (6)

In a flame dried three-neck round-bottom flask was placed sodium hydride (1.2 g, 24 mmol, 50 % dispersion) under N_2 atmosphere. The mineral oil was removed by hexane washing, followed by the addition of (**5**) (1.65 g, 6.0 mmol) in dimethylformamide (20 ml) at 0 °C. The mixture was stirred at 0-30 °C (30 min.). Methyl iodide (0.4 ml, 6.4 mmol) was added to the reaction mixture, stirred for 30 min. at room temperature and acidified to pH = 3. The precipitates were washed and dried to get (**6**). (1.31 g, 20.6 mmol, 86 %); mp 168-169 °C; ν_{max} (KBr) 3320, 3290, 1575, 1350 cm^{-1}; ^{1}H-NMR δ: 11.05 (1H, s, OH), 8.10-7.21 (4H, m, aromatic) 3.75 (3H, s, CH_3); ^{13}C-NMR δ: 34.5, 118.3, 127.7, 128.1, 129.3, 129.9, 132.2, 138.6, 162.1; EIMS *m/z*: 256 [M^+]; Anal. Calcd. for $C_9H_8N_2O_5S$: C, 42.19; H, 3.15; N, 10.93; S, 12.51. Found: C, 42.20; H, 3.14; N, 10.92; S, 12.54

3-bromo-3,4-dihydro-2-methyl-4-oxo-2H-1,2-benzothiazine 1,1-dioxide (8)

A mixture, of (**7**) (2.1 g, 9.9 mmol), N-bromosuccinimide (1.9 g, 11.0 mmol) and azoisobutyronitrile (0.01 g) in carbon tetrachloride (25 ml), was heated under reflux for 1 h, cooled to room temperature and filtered. Evaporation of solvent and recrystallization from ethanol-diethyl ether (50: 50) afforded (**8**) (2.2 g, 7.4 mmol, 75 %); mp 72-73 °C; ν_{max} (KBr) 1680, 1180, 1055 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 8.10-7.22 (4H, m, aromatic), 3.11 (3H, s, CH_3), 2.21 (1H, s , CH); ^{13}C-NMR ($CDCl_3$) δ: 32.4, 79.9, 128.2, 130.7, 130.8, 132.7, 134.4, 140.1, 194.5. EIMS *m/z*: 290 [M^+]; Anal. Calcd. for $C_9H_8BrNO_3S$: C, 37.26; H, 2.78; N, 4.83. Found: C, 37.22; H, 2.71; N, 4.82

4-hydroxy-3-nitro-2-methyl-(2H)-1,2-benzothiazine 1,1-dioxide (6)

A mixture of (**8**) (2.5 g, 8.6 mmol) and sodium nitrite (1.2 g, 17.2 mmol) in dimethylformamide (50 ml) was stirred at room temperature for 5 h, diluted with cold water (250 ml) and filtered. The precipitates were washed and dried to get (**6**) (1.0 g, 3.8 mmol, 45 %); mp 167-168 °C.

One-pot synthesis of 4-hydroxy-3-nitro-2-methyl-(2H)-1,2-benzothiazine 1,1-dioxide (6)

A mixture of (**7**) (2.1 g, 9.9 mmol), N-bromosuccinimide (1.9 g, 11.0 mmol) and azoisobutyronitrile (0.01 g) in carbon tetrachloride (20 ml) was heated under reflux for 1 h. Carbon tetrachloride was distilled out under vacuum. Sodium nitrite (1.31 g, 19.0 mmol) in dimethyl sulfoxide (25 ml) was added and stirred at 50 °C for 2 h. The reaction mixture was cooled, diluted with cold water (200 ml) and filtered to give product (1.4 g, 5.2 mmol, 53 %) mp 166-168 °C.

Conclusion

In conclusion, we present a facile one-pot synthesis of (**6**) in good yield and purity, which can serve as a template for designing new molecules of biological interest.

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